RESEARCH ARTICLE

Impaired associative learning in schizophrenia: behavioral and computational studies

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Abstract Associative learning is a central building block of human cognition and in large part depends on mechanisms of synaptic plasticity, memory capacity and fronto–hippocampal interactions. A disorder like schizophrenia is thought to be characterized by altered plasticity, and impaired frontal and hippocampal function. Understanding the expression of this dysfunction through appropriate experimental studies, and understanding the processes that may give rise to impaired behavior through biologically plausible computational models will help clarify the nature of these deficits. We present a preliminary computational model designed to capture learning dynamics in healthy control and schizophrenia subjects. Experimental data was collected on a spatial-object paired-associate learning task. The task evinces classic patterns of negatively accelerated learning in both healthy control subjects and patients, with patients demonstrating lower rates of learning than controls. Our rudimentary computational model of the task was based on biologically plausible assumptions, including the separation of dorsal/spatial and ventral/object visual streams, implementation of rules of learning, the explicit parameterization of learning rates (a plausible surrogate for synaptic plasticity), and learning capacity (a plausible surrogate for memory capacity). Reductions in learning dynamics in schizophrenia were well-modeled by reductions in learning rate and learning capacity. The synergy between experimental research and a detailed computational model of performance provides a framework within which to infer plausible biological bases of impaired learning dynamics in schizophrenia.

Keywords Learning dynamics · Schizophrenia · Computational models

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Introduction

Schizophrenia is possibly the most complex psychiatric illness and pathology in the hippocampal and prefrontal systems are regarded as central to the disorder (Harrison and Lewis 2001). The role of these systems in associative learning and memory is well established (Toni et al. 2001) and has been emphasized in biologically plausible models (Rolls et al. 2002) that capture interactions between hippocampal sub-units and cortical regions. Models of hippocampal dysfunction in schizophrenia have suggested that lesions in entorhinal to cornu ammonis (CA) region signals, impair context dependent retrieval of paired associates (Siekmeier et al. 2007) suggesting that reduced N-methyl-D-aspartate (NMDA) receptor activity in these

hippocampal regions may underlie impaired memory retrieval. These models have not been designed to explicitly capture learning dynamics or changes in the rate of accumulation of memory. Learning dynamics are crucially related to synaptic plasticity that is, the degree to which synaptic strengths between units are modifiable (Silva 2003). To that end we present experimental results of an object-association learning task in control subjects and schizophrenia patients, and present a computational model of the task designed to model intact and altered learning dynamics. The model is designed to incorporate known principles of neural organization, such as the separation between the dorsal (spatial location) and ventral (object) visual streams (Haxby et al. 1991), the role of the hippocampus as the primary site for the storage of amodal association information (Squire et al. 2004), and standard rules for associative learning (Rescorla and Wagner 1972). Our aim is to present a preliminary framework that captures altered memory dynamics in schizophrenia using a biologically plausible computational model.

Schizophrenia pathophysiology

Schizophrenia is one the most debilitating mental illnesses in the world. Global incidence rates are estimated at between 1% and 2% and the illness has profound personal costs for patients and their families, and widespread societal costs (Murray and Lopez 1996). The illness is widely accepted as being biological (Diwadkar and Keshavan 2003) and developmental in its bases (Keshavan et al. 2006). Decades of biological research have provided convincing evidence of deficits from post mortem studies of brain morphology (Benes et al. 1991; Glantz and Lewis 2000), in vivo brain morphometric reductions (McCarley et al. 1999), function (Kircher and Thienel 2005) and neurochemistry (Keshavan et al. 2000). The genetic bases of the disorder is thought to be complex and heterogeneous, and several candidate genes have been identified particularly those associated with cortical interneuronal monoaminergic signaling, primarily relating to the regulation of glutamate neurotransmission (Harrison and Weinberger 2005).

Dopamine-related and glutamate-related vulnerability can also be associated with abnormal function of the prefrontal cortex and the hippocampus in the illness. Numerous studies have associated impaired dopamine-related prefrontal function and glutamate related hippocampal function as being central to the pathology of schizophrenia (Goldman-Rakic 1999a; Harrison 2004). Abnormal dopamine levels in the prefrontal cortex may directly affect modulation of the excitability of prefrontal neurons (Goldman-Rakic 1999b; Henze et al. 2000) and there is evidence that supra- or sub-normal levels of

dopamine impair working memory (Vijayraghavan et al. 2007; Zahrt et al. 1997). This hyper- or hypo-dopaminergia may cause working memory impairments which are associated with schizophrenia pathology. Further, controlled drug trials in schizophrenia patients have documented the facilitative effects of dopamine enhancing drugs such as risperidone on working memory (McGurk et al. 2005).

Complex glutamate–dopamine interactions may also be implicated (Castner and Williams 2007). The induction of the NMDA antagonist MK801 produces a dose-dependent increase in irregularly discharged single spikes with a concomitant decreases in burst discharges in the prefrontal cortex of freely moving animals. Whereas high frequency discharges are effective in releasing neurotransmitters and therefore central for organized behavior (Lisman et al. 1998), increases in single spike discharges may serve to limit the signal transmission efficiency of prefrontal neurons as well as impair the filtering of irrelevant information (Jackson et al. 2004). Conversely, the in vitro application of NMDA and D1 receptor agonists in prefrontal neurons induces increased inter-spike activity that may lead to the more efficient encoding or processing of information (Durstewitz and Gabriel 2007). Thus altered glutamatergic function may lead to a limitation in the efficiency of processing in the prefrontal cortex, and may be expressed as aberrant increases in functional magnetic resonance imaging (fMRI) measured prefrontal cortical activity in schizophrenia during working memory tasks (Manoach 2003).

Altered NMDA function in the hippocampus has also been implicated in schizophrenia pathophysiology. NMDA receptors (NMDAR) are synaptic coincidence detectors (Bliss and Collingridge 1993) and therefore essential for long term potentiation, which is itself a basis for learning and memory consolidation (Chen and Tonegawa 1997; Shimizu et al. 2000). Reduced NMDAR function has been implicated as a model for schizophrenia pathology (Olney and Farber 1995; Greene 2001; Konradi and Heckers 2003) and in vivo imaging studies have provided evidence of aberrant hippocampal recruitment during tasks of episodic memory (Heckers et al. 1998; Weiss et al. 2003) and memory formation (Achim et al. 2007).

Studies of learning and memory are ideal to understand hippocampal and prefrontal contributions to schizophrenia-related dysfunction, yet few have been applied systematically. Associative learning in particular is a cognitive domain with well-understood implementations in the hippocampus (Buchel et al. 1999), and associations with the glutamatergic system (Silva 2003). Studies have suggested that learning impairments are a marker of hippocampal impairment in schizophrenia (Wood et al. 2002). Furthermore, computational models of hippocampal function in the service of learning and memory have richly captured

the interactions between the region's sub-units (Rolls 1996) and have begun to be applied to cognitive impairment in schizophrenia (Siekmeier et al. 2007). Below we briefly review the bases of associative learning and memory in the brain before describing computational simulations of a formal model designed to capture bases of learning impairment in schizophrenia.

Associative learning and memory in the brain

Associative learning and memory are cornerstones of human and animal cognition with relevance to the several other cognitive domains. For example, the ability to associate memoranda with each other or with context underlies successful spatial navigation in the rodent (Poucet and Benhamou 1997) and spatial learning in the primate (Brasted et al. 2003). Associative memory and learning are also related to a wide variety of skill acquisition tasks in the human and have been associated with successful lexical acquisition in human imaging studies (Breitenstein et al. 2005). The central role of associative learning and memory in cognition can be understood based on the key role of the medial temporal lobe and its sub-structures in these processes, and the placement of the medial temporal lobe in the hierarchy of connectivity across the uni- and hetero-modal pathways in the brain (Lavenex and Amaral 2000; Mesulam 1998).

The weight of experimental evidence clearly indicates that the medial temporal lobe, including the hippocampus and its sub-units such as the CA, the dentate gyrus (DG) and the subiculum, and adjacent structures such as the entorhinal cortex are central to the initial formation of long term associative memories. These regions occupy a unique anatomical place within the realm of cortical and sub-cortical connections receiving inputs from the sensory areas in unimodal association cortex and from heteromodal areas such as the dorsal and ventral prefrontal cortex via the entorhinal cortex. The medial temporal lobe is therefore uniquely positioned to integrate inputs from uni- and hetero-modal areas before redistribution of potentiated associations into the neo-cortex (Eichenbaum 2001). This general framework provides a good explanation for the patterns of anterograde amnesia in classic neuropsychological studies of patients with hippocampal lesions (Scoville and Milner 1957) in which the retention of memories before the lesion is preserved but the formation of new long term memories is impaired. It also is consistent with experimental work in animals: Lesions that are applied to the hippocampus early during learning devastate trace conditioning preventing eventual consolidation of traces in long term memory (Takehara et al. 2003). When the function of the medial temporal lobe is impaired during

learning of associations, memorial representations that rely on this hippocampal activity are either not formed, or are formed to inadequate strength (Squire et al. 2004). Thus, memory is inadequately established and is unavailable at the fidelity needed when recall is required.

In the human brain, the interplay between evolutionarily mature prefrontal and hippocampal regions underlies associative learning. Whereas the precise contributions of each of these regions is the subject of debate (McClelland et al. 1995), conscious associative encoding may involve persistent prefrontal activity needed to maintain representations in working memory (Hazy et al. 2007). Concurrent activity within the medial temporal lobe may be needed to create a-modal traces of bound associations (Law et al. 2005). Experimental work using in vivo imaging studies has highlighted the involvement of both the hippocampus and prefrontal cortex in memory encoding and retrieval (Simons and Spiers 2003). Separate studies of behavioral pharmacology have identified molecular mechanisms for associative learning. Activity of the N-methyl-D-aspartate (NMDAR) receptor and its sub-units (NR1-2) in the hippocampus are specifically implicated (Chen and Tonegawa 1997). The NMDAR is thought to endow long-term potentiation with Hebbian characteristics, by allowing electrical events at the postsynaptic membrane to be transduced into chemical signals. These in turn activate pre- and postsynaptic mechanisms to generate a persistent increase in synaptic strength. The increased synaptic strength is a hallmark of associative learning as outlined in early formal theories (Hebb 1949). (For a review on post-Hebbian algorithms see Érdi and Somogyvári 2002). Thus, the interplay between prefrontal and hippocampal systems may have complex neurochemical bases characterized by interactions between the D1 receptor of the dopaminergic system and the NMDAR (Castner and Williams 2007).

Single unit recordings and fMRI studies have extensively documented hippocampal involvement during associative encoding and retrieval. For example, spike rate activity in hippocampal neurons increases with success in encoding, with a categorical shift in activity from sub- to supra-threshold behavior following successful encoding (Wirth et al. 2003). Furthermore, sharp increases in fMRI-measured activity in the hippocampus are observed during associative memory tasks (Law et al. 2005; Zeineh et al. 2003) and studies have demonstrated the critical dependence on the hippocampus in tasks of object-location association (Milner et al. 1997).

Neurobiological background of the learning model

The model incorporates several crucial biological aspects based on experimental data in humans (controls and

patients) and animals. In particular, we take into account that (i) there is a separation between ''where'' and ''what'' regions; (ii) synaptic plasticity is reduced for patients and (iii) patients show reduced cognitive performance. These points are further expanded on below.

(i) Primate studies indicate a general separation of the extra-striate visual streams into the dorsal (spatial location, parietal cortex) and ventral (object identity) pathways (Ungerleider 1995). This separation and cooperation between systems is consistent with in vivo imaging studies that suggest relative specialization of the dorsal stream (parietal systems) for the processing of spatial information, and of the ventral stream for the processing of object identity (Sommer et al. 2005). Any biologically plausible model of object-location learning must preserve the functional and structural separation between these classes of inputs. Because of the role of the hippocampal formation and its sub-units, particularly the entorhinal cortex, the DG and the CA (Lavenex and Amaral 2000) in consolidating associations, these regions serve as the repository of amodal associations over intermediate time scales (such as are employed in the experimental paradigm). Therefore, a model of learning must incorporate a neural mechanism to bind associations between disparate modal inputs.

(ii) Synaptic plasticity is a central mechanism that is necessary to achieve associative learning (Chen and Tonegawa 1997). For example, synaptic plasticity within hippocampal sub-units is a central determinant in the efficacy of learning and memory (Silva 2003), and reduced synaptic plasticity is a potential characteristic of altered functional organization in schizophrenia (Konradi and Heckers 2003, Stephan et al. 2006). Therefore parameters that govern the rate of change of associative strengths may be central to modeling deficits in learning in schizophrenia. Such parameters need not encapsulate processing assumptions regarding the supervisory role of regions such as the prefrontal cortex in the manner of other models of learning and memory (Hazy et al. 2006; O'Reilly and Frank 2006). However they can provide a quantitative parameterization of upstream (hippocampus to frontal cortex) and/or downstream (frontal cortex to hippocampus) modulations of memory encoding that underlie associative learning.

(iii) Studies suggest limitations in peak performance ability in schizophrenia. Schizophrenia patients show reduced working memory capacity (Jansma et al. 2004) that may be related to reduced gamma-frequency synchronized neuronal activity in pre-frontal GABA neurons (Lewis et al. 2005), as well

as reduced structural and functional capacity of the hippocampus (Heckers 2001). Therefore, parameters that reflect capacity limitations may be essential to capturing intrinsic differences in performance limits between the healthy and the schizophrenia brain.

The aim behind modeling is to capture dynamic neural principles in a computational framework that permits experimentation and synergies with experimental data (Hasselmo and McClelland 1999). The application of computational models to schizophrenia function has been relatively sparse but several informative efforts exist. For example, neural network simulations have documented hallucinatory outputs following elimination of working memory synapses, providing an informative existence proof of how excessive prefrontal synaptic pruning (Keshavan et al. 1994) may give rise to cognitive and phenotypic characteristics in schizophrenia (Hoffman and McGlashan 1997). Modeling efforts can characterize network interactions in regions of the associative memory network in terms of changes in parameter values that represent biologically relevant processes such as synaptic strength or firing rates. Models can therefore provide an explanatory framework for integrating empirical data in control and schizophrenia behavior and be predictive of behaviors in other cognitive domains.

Below we present an explanation of the experimental task with detailed specification of the model, and its processing constituents as they relate to the general and specific principles of neurobiology of the healthy and the schizophrenia brain. These descriptions are followed by presentations of empirically achieved results from control and schizophrenia patients as well as a characterization of model behavior in different regions of the parameter space that define "control" and "schizophrenia" performance. These simulation results give insight into the normal and pathological neural mechanisms of the associative learning task presented.

Methods

Subjects

Healthy controls ($n = 11$; mean age = 22 years, sd = 5; 5 females) and stable early course patients diagnosed with schizophrenia or schizoaffective disorder ($n = 11$; mean age = 26 years; sd = 5; 3 females) gave informed consent to participate in the protocol approved by the Wayne State University Human Investigative Committee (HIC). Groups did not differ in terms of age ($P > 0.10$). Patients were diagnosed using DSM-IV, SCID and consensus diagnosis.

All were on a regimen of atypical antipsychotics (Risperidone, Olanzapine or Aripiprazole), were recruited from the Services for Early Treatment of Psychosis program at Wayne State University and were in the early stages of their illness (<5 years). Subjects were paid for their participation.

Experimental methods

Subjects participated in an associative learning/memory task adapted from previous studies (Buchel et al. 1999). During the course of the task, subjects learned the associations between nine equi-familiar objects drawn from a standardized battery (Snodgrass and Vanderwart 1980) over a series of encoding/consolidation and retrieval epochs. During each epoch, objects were presented in their associated location in space (3s/object) for naming. All nine objects were shown in random order. Following a brief rest interval, the nine locations were cued (with a square) in random order and subjects were required to recall the object associated with the location. Eight blocks (each cycling between encoding, rest and retrieval) were employed. A schematic of the task is depicted in Fig. 1.

Computational modeling

The preliminary model is designed to simulate the behavioral associative learning task, and final model output is learning curves that depict output over each iteration of recall. As will be evident, the model incorporates the separation between encoding/consolidation and cued recall while also retaining biological plausible relationships between model architecture and neural systems, as well as known learning parameters in the brain.
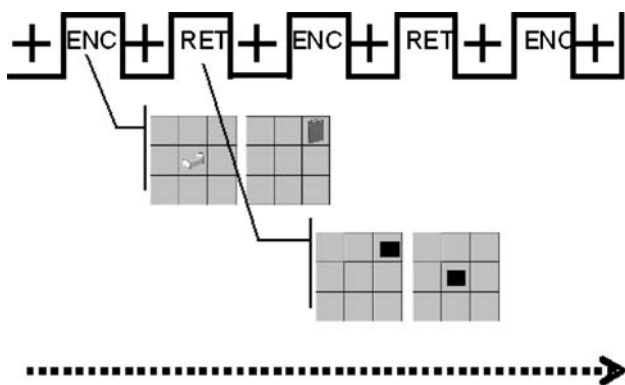
Fig. 1 Structure of the experimental paradigm is depicted with two examples of associations presented during encoding/consolidation ("bed" and "book") and examples of those locations cued during recall/retrieval

Encoding/consolidation

Separate neural systems are represented by two separate nine dimensional binary vector inputs supplied to the model representing the object shown to the subject and the location of the object named a_L and a_O respectively. Nine unique object–location vector pairs for each trial represent the nine unique object–location relationships in the task. A normally distributed noise term with positive values and a mean of 0.5 is added to each element to simulate background neural activity in the brain and to remove binarization of the input vectors. The mean of the noise term is not trivial and is chosen in relation to the other model parameters to provide acceptable results.

Each vector pair is dyadically multiplied to form a single object–location association matrix A, which has elements that fall into three categories. The element that results from multiplying the active signal of a_L and a_O contains the strongest association. Every other element in the row and column that it occupies is the product of active signal and a noise term. The remaining elements, those that are not in the row or column of the active signal, are the product of only noise terms and contain no meaningful signal.

Each A is added to form $W(t)$. Because of the uniqueness of the objects and locations in a_L and a_O, $W(t)$ only exhibits two different types of elements.

$$W(t) = \sum_{t=1}^{9} A_i \tag{1}$$

As each object and location in a trial occupies a different component in the respective a_L and a_O, each column and row of $W(t)$ has a term that has active signal with added noise. The remaining elements in $W(t)$ are terms of signal multiplied by noise with added noise. $W(t)$ has nine elements that hold correct multiplicative associations with noise and 72 elements that hold incorrect additive associations. $W(t)$ is multiplied by a learning rate $r(t)$ that modulates the strength of associations on a trial-wise basis to form $W(t + 1)$. The computation underlying the encoding matrix is described in Eq. 2.

$$W(t + 1) = r(t)\,W(t) \tag{2}$$

where $W(0)$ equals the zero matrix.

The Rescorla–Wagner based learning rule used is described in Eq. 3.

$$r(t) = r_{max}(S_{max} - S(t = 1)) \tag{3}$$

As seen in Eq. 3, the learning rule $r(t)$ is a function of a learning rate coefficient, r_{max}, the maximum possible performance, S_{max} and the performance of the subject on the previous iteration, $S(t - 1)$. The learning rate coefficient r_{max} is a parameter that depends on the state of the subject (control or patient). Both groups of subjects

show monotonically increasing performance over time, that is, incremental learning. Therefore as $S(t - 1)$ increases, $r(t)$ will generally decrease as t increases, that is over several iterations of the task.

During encoding in Eq. 2, the learning rate $r(t)$ functions as a supervisory parameter by modulating the strength of the encoding matrix W at any instant during learning, depending on its own parameterization in Eq. 3. Crucially, at any given time t during learning the association matrix $W(t)$ represents the strengths between associations to be learned during the task.

Recall

During recall, the model is given a noiseless input a_L which represents the location cue (see Fig. 1). a_L is multiplied with the encoding matrix $W(t + 1)$ to select the column of $W(t)$ that contains the information of which object is associated with the chosen a_L. This recalled column is a vector y in Eq. 4:

$$y = a_L W(t) \tag{4}$$

Each element in y must be evaluated to determine if it is an active recall or a noise induced value. A threshold τ is used to make this discrimination:

$$\tau : \frac{1}{81} \sum_{i=1}^{9} \sum_{j=1}^{9} W_{ij}(t + 1) + \pi[\max(W(t + 1))] \tag{5}$$

where i is a column of $W(t)$ and j is a row of $W(t)$ and π is a chosen multiplier between 0 and 1. The threshold is determined by averaging the elements of $W(t)$ and adding the largest element in $W(t + 1)$ multiplied by π. This premium controls the sensitivity of the model to noise.

Results

Behavioral results

Figure 2 depicts mean experimentally derived performance (percentage of correct associations retrieved) as a function of epoch (1 to 8) for each of the two groups. Behavioral data were lost for three subjects on account of experimenter error. Behavioral data were analyzed to: (a) approximate learning functions for each group and (b) assess differences between groups in learning potential and rate. Patients learn at a slower rate than controls, but show monotonic increases in performance, suggesting (sub-optimal) engagement of memory consolidation systems. To increase power to assess differences between groups we analyzed performance as a function of "early" vs. "late" recall (denoted in Fig. 2). "Early" to "Late" performance in both
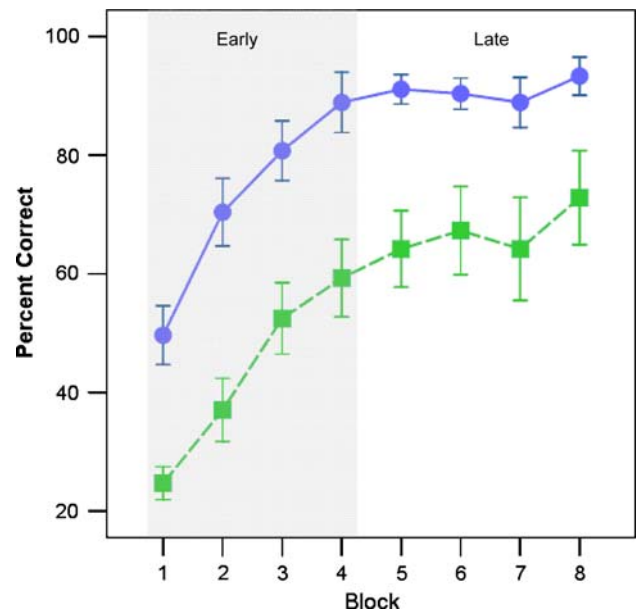
Fig. 2 Learning dynamics in controls and schizophrenia patients over time are plotted. The data provide evidence of generally asymptotic learning in both groups, with reduced learning rates in patients compared to controls. Shaded area depicts "early" learning period and unshaded area depicts "late" learning period. Error bars in the graph are ±sem

groups increased with patients showing impaired consolidation during both periods, $F_{1,16} = 10.33$, $P < 0.01$.

Simulation results: parameter space for r_{max} and S_{max}

The strength of associations in the association matrix W is principally determined by two parameters: (a) the learning rate r_{max} which can represent biological relevant features such as the degree of synaptic plasticity and (b) the maximal learning capacity S_{max} which may represent constraints on memory capacity in controls and patients. To understand the model's behavior, we assessed the two-dimensional parameter space for regions of plausible and implausible performance. As seen in Fig. 3, parameter values for simulations evinced three regions in the parameter space: (a) plausible performance regime for control subjects, (b) plausible performance regime for "schizophrenia" patients and (c) implausible performance regime. The degree of plausibility was estimated by comparing model and behavioral results.

To explain the bases of implausible model behavior we detail three main classes under which such behavior is achieved: (a) A high r_{max} with a low S_{max}: these parameter conditions reveal immediate saturation in performance but with low levels of retention of associations. (b) Low r_{max} with a low S_{max}: under these conditions, the model fails to learn the associations as the learning threshold is never exceeded. This pattern of model behavior is observed near
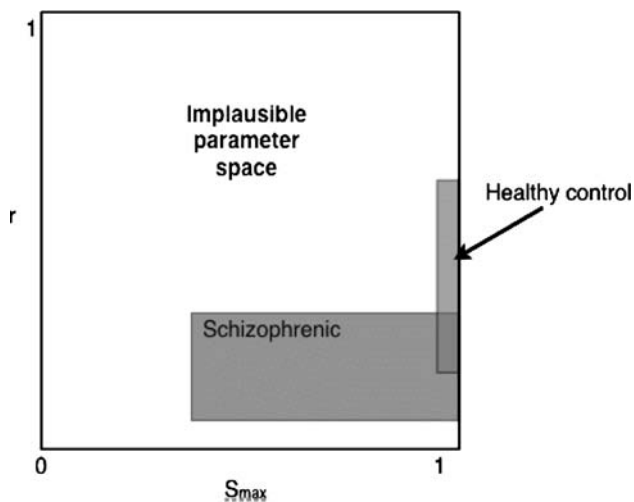
Fig. 3 Parameter space for r_{max} and S_{max} with approximate plausible regions labeled for healthy controls and "schizophrenia" patients

the limits of the plausible range of "schizophrenia" behavior, (c) High r_{max} and high S_{max}. This pattern is seen when these parameters values are near maximal and lead to rapid behavioral saturation with perfect retention.

Simulation results: parameter space for noise and threshold (π)

In addition to r_{max} and S_{max} behavior of the model is also governed by π and the noise term. There is a narrow range of values of these parameters where learning occurs at a realistic rate. The plausible threshold values are centered at 0.53 and in the range $0.4 \leq \pi \leq 0.6$. Noise values should be lower than 0.3 when the threshold is greater than 0.53 and greater than 0.3 when the threshold is lower than 0.53. When there is too little noise, recall values will approach one, and when the threshold is high, relative to noise, recall values become smaller.

Any value in y which is greater than τ is reassigned a value of one, indicating active recall. Those below τ are given a value of zero, indicating a noise induced value. This returns the recall vector to a binary state (y_τ), so it can be compared to a perfect response vector a_O. It is possible that the model will return more than one active recall for a given location. In this case, the recall is treated the same as an incorrect recall. For each vector the elements in y_τ corresponding to the perfect response vector are counted and divided by the number of associations (9). This provides a score between 0 and 1 that indicates the correctness of the subject's recall. The learning and recall stages are repeated for all subjects and the scores are averaged over subject group to obtain learning curves.

A narrow range of simulations achieved under varying conditions of noise and π are depicted in Fig. 4 and the

parameter space of noise to π governing plausible recall performance is depicted in Fig. 5.

Healthy control performance

For healthy controls, the plausible parameter range for r_{max} was 0.2 to 0.55. As shown in Fig. 3, the plausible maximum performance or S_{max} approaches one on this task as perfect performance by the 8th iteration is within the range of control performance. The representative healthy control parameters were $r_{max} = 0.4$ and $S_{max} = 1$, yielding a behavior curve similar to achieved control data. The plausible parameter range can be estimated by looking at the maximum and minimum values given by the ideal parameters and determining the parameter values that will give, on average, the maximum and minimum values for an average healthy control subject. Figure 6a shows the performance of the model based on ideal parameter values.
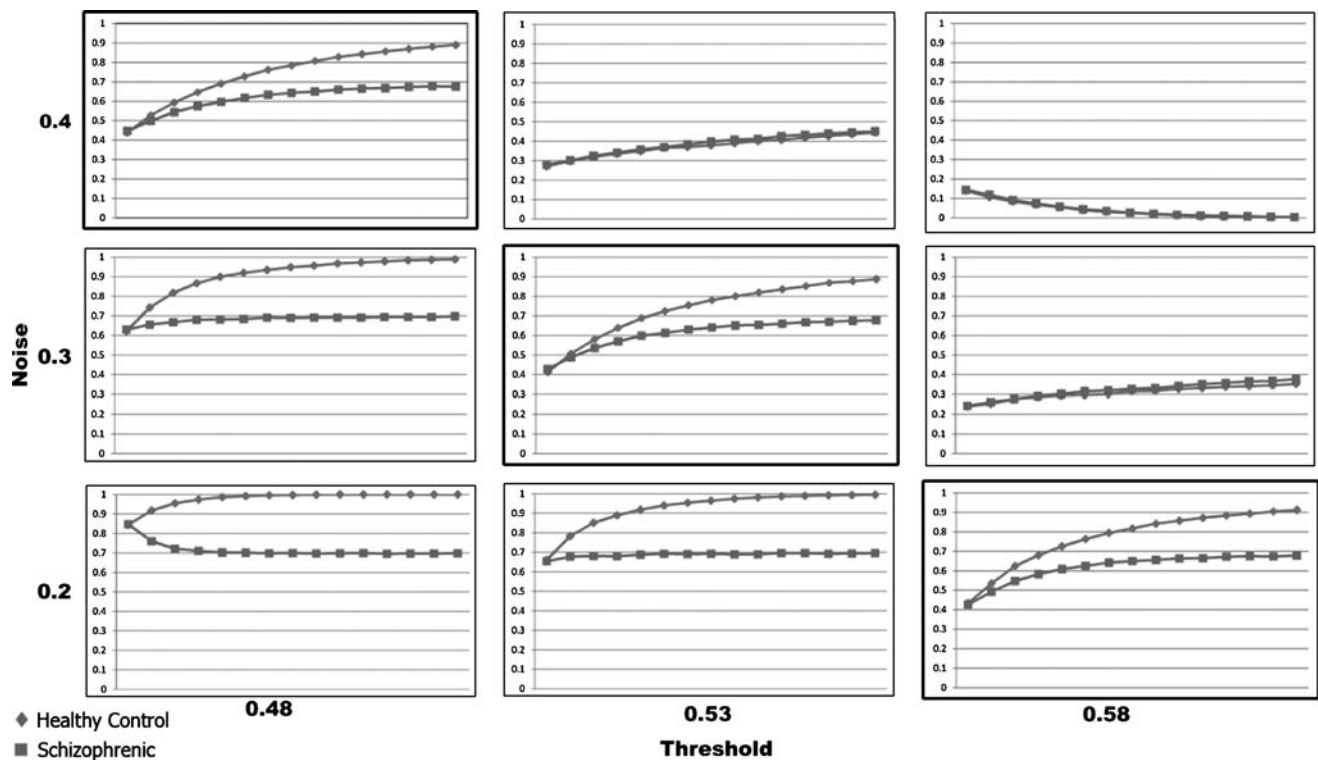
"Schizophrenia" performance

For "schizophrenia" like performance, the plausible parameter range for r_{max} was 0.1 to 0.25 with representative performance achieved for $r_{max} = 0.2$ and $S_{max} = 0.7$. Figure 6b depicts average and range of performance for schizophrenia behavior.

Discussion

Several observations result from the simulation of the model. Firstly, there is overlap in the plausible parameter values (Fig. 3) for healthy control subjects and schizophrenia patients. This reflects the idea that schizophrenia performance in several cognitive domains may reflect capacity limitations resulting in partial overlap with healthy control performance. This was observed in the achieved experimental data (Fig. 2) where partial overlap in performance (particularly during the early stages of learning) was observed. Secondly, the simulations provide reasonable representations of achieved empirical data including both monotonicity in performance as well as the separation between control and schizophrenia performance. Finally, these distinctions in performance are largely captured by systematic differences in the biologically plausible parameters r_{max} and S_{max} that may reflect meaningful constraints on the rates and capacity of associative learning by biological differences between the schizophrenia and control brain.

The interaction between r_{max} and S_{max} is particularly noteworthy in its consistency with studies on animal and human learning. r_{max} is a learning rate coefficient governing processes that can represent synaptic plasticity. The

◆ Healthy Control
■ Schizophrenic

Fig. 4 A subset of simulations depicting model performance as a function of noise and threshold (π) parameters. Note the results along the diagonal that depict plausible performance for "control" like behavior (diamond markers) and "schizophrenia" like behavior (square markers). Note that the simulations extend beyond the eight iterations that are used in the rest of the reported model behavior
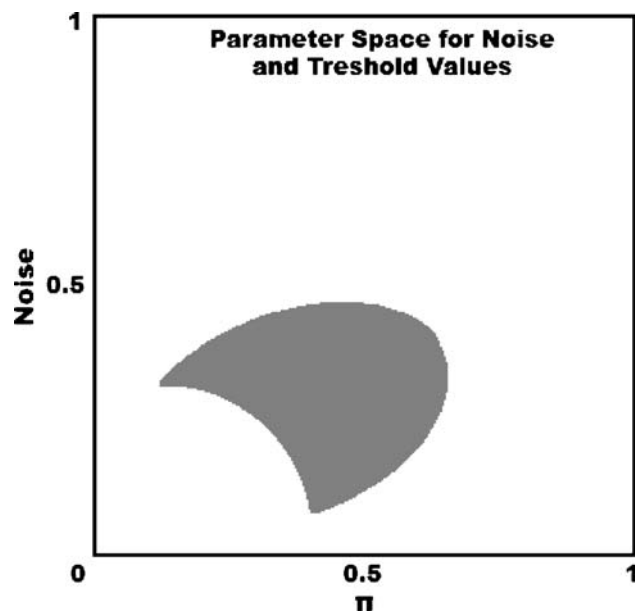

Fig. 5 The plausible parameter space for model performance under different values of noise and threshold (π)

induction of long-term synaptic plasticity in hippocampal synapses has been shown to govern hippocampal place memory in rodent studies (Nakazawa et al. 2004), and may also relate to the increased intra-hippocampal synchrony in

neuronal outputs that has been documented during the early stages of learning (Cheng and Frank 2008). It has been argued that altered synaptic plasticity related to NMDAR dysfunction is central to the disconnection syndrome of schizophrenia (Stephan et al. 2006) though to our knowledge no direct evidence from human or animal models of schizophrenia have demonstrated this. Our ongoing fMRI studies related to the current task have provided evidence of altered plasticity of the BOLD response in the hippocampus and the prefrontal cortex and may provide future clarification.

S_{max} reflects capacity constraints on memory, consistent with the widely accepted view that capacity constraints on memory and attention govern human memory performance (Chun and Turk-Browne 2007). A reduction in working memory capacity related to diminished gamma frequency neuronal synchrony in prefrontal cortex has been proposed as underlying reduced working memory capacity and ability in schizophrenia (Lewis et al. 2005). However, to our knowledge, no definitive behavioral studies of hippocampal-related memory exist. Given that prefrontal and hippocampal interactions are central to processes of associative memory encoding and recall (Simons and Spiers 2003), in this rudimentary stage of our model, S_{max} can be viewed as a representation of general memory constraints in schizophrenia.
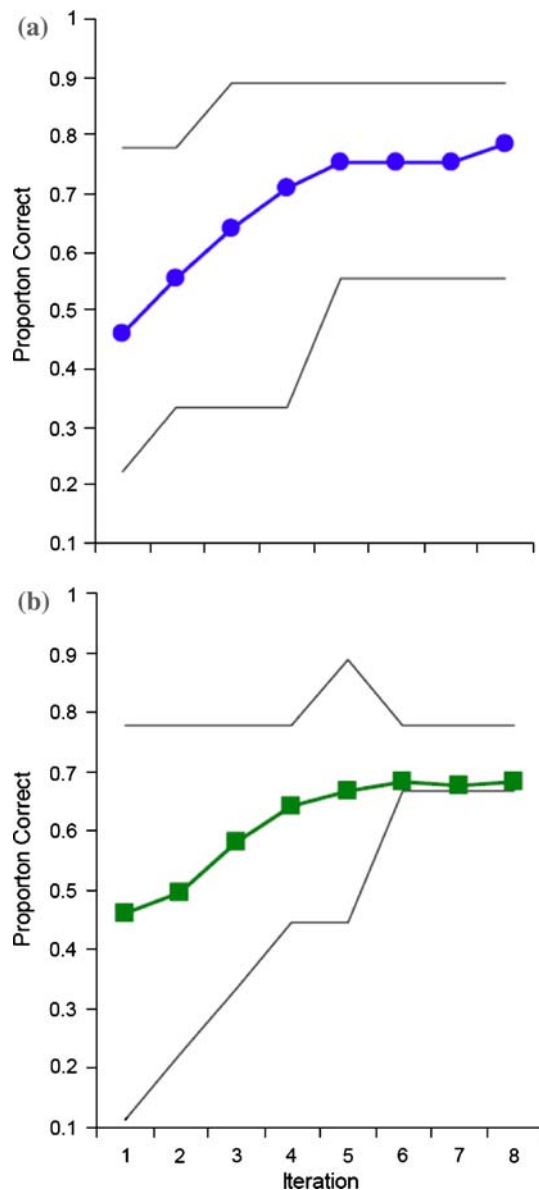
Fig. 6 (**a**) Maximum, minimum, and average values for healthy control patients. Produced with parameter values $S_{max} = 1$ and $r_{max} = 0.4$. Maximum and minimum curves are the basis for finding the parameter ranges. (**b**) Maximum, minimum, and average values for "schizophrenia" patients. Produced with parameter values $S_{max} = 0.7$ and $r_{max} = 0.2$

Future models of fronto–hippocampal function in schizophrenia: mechanisms of impairment

Models of the disordered brain must capture mechanistic interactions between brain regions that ideally span across levels of description. For example, extensive animal work has identified pathways within the medial temporal lobe associated with specific aspects of learning and memory. Studies suggest that the DG performs pattern separation by competitive learning (McHugh et al. 2007): it removes

redundancies from the input to produce a sparse representation for learning in the CA region (specifically the CA3 sub-field). This process can be considered as translating information from neocortical to hippocampal space. Granule cells in the DG innervate CA3 pyramidal cells with particularly large and efficient synapses (the mossy fiber pathway) that make postsynaptic neurons fire (Treves and Rolls 1994). These mechanisms are fundamental to learning and memory dynamics and can be modeled not only at the level of synaptic interactions between medial-temporal lobe network constituents but may also incorporate pharmacologic parameters (Aradi and Érdi 2006). Formal models may be developed to capitalize on the known relationship between glutamatergic (Aiba et al. 1994) and cholinergic function (Hasselmo 1999), and learning and memory consolidation. For example, acetyl-choline enhances the rate of synaptic modification in the cortex (Skrebitsky and Chepkova 1998) which is itself related to long-term potentiation and learning dynamics; Models that incorporate acetylcholine antagonists such as scopolamine (Hasselmo and Wyble 1997) have been successfully employed to explain impaired recall during list learning tasks. Similarly, mechanistic models of cortico–hippocampal function that incorporate glutamatergic receptor function are likely to provide important insights on dysfunction in schizophrenia (Grunze et al. 1996). Furthermore, these models must scale to also incorporate macroscopic in vivo functional data such as fMRI that capture neuronal interactions at the level of pools of neurons rather than single unit activity (Logothetis 2002). Our ongoing efforts are proceeding in parallel: the development of mechanistic models of fronto–hippocampal function and the exploration of dynamic causal models that are designed to capture fMRI activation dynamics across brain regions (Stephan et al. 2007).

In contrast to the abstract neural network model presented here, our ongoing approaches will center around neural computational models based on known hippocampal circuitry (Rolls 1996). These mechanistic models distinguished between a simple retinotopic visual system, and a more detailed articulation of the hippocampal formation. Feed-forward networks will analyze the retinal image, and create object and location representations in the inferior temporal and superior parietal cortices respectively. The role of the hippocampus is to bind these two representations together (Milner et al. 1997) so that object recollection can proceed with a location cue.

In the current version, highly processed sensory input enters the hippocampus through the mossy fiber pathway, originating in the entorhinal cortex. The entorhinal cortex is itself modeled through reciprocal connections with both hippocampus and various neocortical regions, including visual areas, and is considered a relay for information

arriving from multimodal association areas. These assumptions are consistent with the known hierarchy of processing within the medial temporal lobe structures (Lavenex and Amaral 2000). Mossy fibers terminate on the DG granule cells and hippocampal pyramidal neurons. Two regions of the hippocampal formation are currently incorporated in the working model: the DG and the CA3 region. Activation of each unit is calculated by the linear sum of its input using known firing rate models (Booth and Bose 2001). Synaptic connections in the inferior temporal cortex, DG and CA3 region are modified by simple Hebbian plasticity. Current simulations involve large numbers of neurons (typically ∼500 in one layer) in order to implement distributed encoding in a realistic range of sparseness (0.1 in the hippocampus). The capacity of the system with 500 units and 0.1 sparseness is a few hundred associations (by an order of magnitude fewer than what is ecologically viable). However, with random initial synaptic weights and a small learning rate, the model requires some repetitions to learn new associations appropriately. Initial simulations have addressed the effects of the depth of the inferior temporal attractor basin (shallower vs. deeper) and hippocampal learning rates on model performance. This work however is in a preliminary stage and our ongoing efforts will help clarify the precise nature of hippocampal involvement and of contributions from supervisory regions such as the frontal cortex (Hazy et al. 2007).

The current modeling work is also taking place together with fMRI studies to understand the neural bases of disordered learning in schizophrenia. Whole brain fMRI affords the ability to collect surrogate markers of neuronal activity with a reasonable balance of spatial and temporal resolution (Niessing et al. 2005). Furthermore, interactions between brain regions can be inferred using techniques to estimate functional or effective connections (Horwitz et al. 2005). Our parallel effort use dynamic causal modeling to solve the "inverse problem" in fMRI, that is to estimate effective connectivity parameters. Effective connectivity describes causal influences that cortical regions or neuronal units exert over each other (Friston et al. 2003). Effective connectivity can be derived based on a priori assumptions regarding the order of information flow between neuronal units, and the influence exerted by the neuronal units on each other. The "causal" bases of such modeling are therefore self-evident.

We aim to establish a causal model with five significance components, specifically the primary visual cortex, the superior parietal cortex, the inferior-temporal cortex, the hippocampus and the prefrontal cortex. The choice of these regions parallels our computational modeling efforts and will allow us to understand the generation of normal and pathological temporal patterns in the collected fMRI data. This model framework would address impaired connections in schizophrenia, and the measure of functional reduction of the information flow.

Conclusions

The modeling results reported in this paper are the initial efforts to begin a general program that uses in vivo imaging and computational modeling to understand functional pathology in the schizophrenic brain. The reported results are limited, yet indicate how limitations/changes in synaptic plasticity and memory capacity can predict control or schizophrenia-like behavior in learning and memory dynamics. The extension of these results to *process* models of frontal–hippocampal-unimodal interactions will provide stronger bases for these findings and provide increased translational relevance to animal studies of synaptic plasticity and learning in the brain. Our in vivo studies of changes in the neural response measured with BOLD associated with learning dynamics (Diwadkar et al. 2008; Murphy et al. 2008) indicate that whereas the BOLD response in key hippocampal sub-regions such as the CA and the DG decreases with increased memory proficiency in controls, this pattern of BOLD plasticity is absent in patients. Further, time-related increased functional connectivity (Friston et al. 1997; Buchel et al. 1999) with learning between the hippocampus and prefrontal cortex is observed in controls, whereas this pattern is absent in patients. These fMRI findings of altered plasticity and reduced connectivity provide general convergence with our current modeling results. However, our emerging synergy (fMRI, behavior, and modeling) will help to further elucidate the nature of altered learning dynamics in schizophrenia, the relationship of these alterations to molecular mechanisms, and ultimately we anticipate to neuropharmacology and mechanisms of drug discovery (Aradi and Érdi 2006; Javitt et al. 2008).

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